REMARKS

The above amendments to the specification and the claims have been made to include substitute pages of the specification reflecting the changes made under PCT Article 34 amendment, to adapt the claims to U.S. format and to place the application in better condition for examination. An English translation of the PCT Article 34 Amendment is enclosed.

If any fees are due in connection with this paper, please charge our Deposit Account No. 50-2866.

Respectfully submitted,

WESTERMAN, HATTORI, DANIELS & ADRIAN, LLP

Stephen G. Adrian
Attorney for Applicants
Registration No. 32,878
Telephone: (202) 822-1100
Facsimile: (202) 822-1111

SGA/yap

(non-patent document 1, p.590, right column, ll.7 to 3 from bottom, and fig.30). The said document also suggests that GsMTx-4 has an ICK motif with a basic structure defined by three cysteine pairs (C_1-C_4, C_2-C_5 and C_3-C_6) (non-patent document 1, p.595, left column, l.7 to 1.11 from bottom, column 'The structure of GsMTx-4').

Furthermore, methods for extracting and purifying GsMTx-4, methods for treating cerebral arrhythmia with the said GsMTx-4 and so forth have been suggested (see for example Bode et al., Nature, Vol.409, pp35-36 (2001) (non-patent document 2), US Patent Application Published Description No.2002/0077286 (patent document 1)). Further, the structure of GsMTx-4 has been known from results obtained in a solution using NMR (see Robert et al., J. Biol. Chem. Vol.37, pp3443-3445, 2002. (non-patent document 3)). Despite such findings, a remedy for atrial fibrillation using the peptide derived from spider venom (GsMTx-4) had not been developed.

References

Patent document 1: US Patent Application Published Description No.2002/0077286;

Non-patent document 1: Thomas M. Suchyna et.al., Identification of a Peptide Toxin from Grammostola Spatulata Spider Venom that Blocks Cation-selective Stretch-activated Channels, J. Gen. Physiol., Vol.115, pp583-598 (2000);

Non-patent document 2: Bode et al., Nature, Vol.409, pp35-36 (2001);

Non-patent document 3: Robert et al., J. Biol. Chem. Vol.37, pp3443-3445 (2002).

The object of the present invention is to identify the pharmacophore (the minimum space structure needed for activation) of GsMTx-4, to design novel polypeptides that specifically inhibit the activity of a mechano-sensitive channel based on the pharmacophore information, and to provide remedies for atrial fibrillation consisting of such polypeptides.

SUMMARY OF INVENTION

The above objects are achieved by the following inventions.

[1] In a first aspect of the present invention, it involves a polypeptide or salts thereof consisting of an amino acid sequence represented by SEQ ID NO:1 or SEQ ID NO:2, and forming an intermolecular disulfide bond between two of the cysteines contained in SEQ ID NO:1 or SEQ ID NO:2. These polypeptides, as confirmed in the embodiment of this description, are polypeptides that show mechano-sensitive channel inhibiting activity, and can be considered as polypeptides that compose the pharmacophore of GsMTx-4. These

polypeptides are useful for treatment of atrial fibrillation and such.

[2] In a second aspect of the present invention, it involves a polypeptide or salts thereof comprising an amino acid sequence represented by SEQ ID NO:1 or SEQ ID NO:2, not having an amino acid sequence represented by SEQ ID NO:4, and forming an intermolecular disulfide bond between two of the cysteines contained in SEQ ID NO:1 or SEQ ID NO:2.

[3] In a third aspect of the present invention, it involves a polypeptide or salts thereof consisting of an amino acid sequence represented by SEQ ID NO:1 or SEQ ID NO:2, of which one or several of the amino acids thereof have been deleted, substituted, inserted or added, also forming an intermolecular disulfide bond and moreover showing mechano-sensitive channel inhibiting activity.

[4] In a fourth aspect of the present invention, it involves the polypeptide or salts thereof described in the above [3] as consisting of an amino acid sequence represented by SEQ ID NO:1 or SEQ ID NO:2 of which one or more of the amino acids thereof have been deleted, substituted, inserted or added, of which the said amino acid sequence is an amino acid sequence represented by SEQ ID NO:16 or SEQ ID NO:17.

[5] In a fifth aspect of the present invention, it involves a polypeptide or salts thereof consisting of an amino acid sequence represented by SEQ ID NO:16 or SEQ ID NO:17. These polypeptides, as confirmed in the embodiment of this description, are polypeptides that show mechano-sensitive activity. These polypeptides are useful for treatment of atrial fibrillation and such.

[6] In a sixth aspect of the present invention, it involves a polynucleotide comprising the polynucleotide that encodes the polypeptide described in the above [1] as consisting of an amino acid sequence represented by SEQ ID NO:1 or SEQ ID NO:2, and forming an intermolecular disulfide bond between two of the cysteines contained in SEQ ID NO:1 or SEQ ID NO:2, of which the said polypeptide comprises an amino acid sequence represented by SEQ ID NO:2, encodes the polypeptide described in the above [3], or encodes the polypeptide described in the above [5].

[7] In a seventh aspect of the present invention, it involves a recombinant vector comprising the polynucleotide described in the above [6].

[8] In a eighth aspect of the present invention, it involves a transformant transformed by the recombinant vector described in the above [7].

[9] In a ninth aspect of the present invention, it involves a mechano-sensitive channel inhibitor comprising one or more of the polypeptides or salts thereof described in one of the above [1] to [5]. This inhibitor specifically inhibits the activity of a mechano-sensitive channel and thus is useful for conducting researches on mechano-sensitive channels and such.

[10] In a tenth aspect of the present invention, it involves a remedy for atrial fibrillation comprising one or more of the polypeptides or salts thereof described in one of the above [1] to [5]. These polypeptides, as confirmed of their functions in the embodiment